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DR. ROSCOE GRAHAM

Dr. Roscoe Reid Graham died at Collingwood, where he had been skiing, on January 17th. He was 58 years of age. His death was a great shock to his colleagues, students and friends since until the moment when he died he had seemed in perfect health.

Dr. Graham was born at Lobo, near London, Ontario, on January 2nd, 1890. He was the son of Dr. Peter Graham, a fine type of country practitioner, whose influence was such that his three sons chose medicine as a profession. One brother, Dr. Stanley Graham is professor of paediatrics at the University of Glasgow, the other, Dr. Wilfred, practised surgery in Vancouver until his death a year ago.

Dr. Roscoe Graham graduated from the University of Toronto in 1910. He spent one year as an interne at St. Michael's Hospital where he came under the influence of the late Dr. Gideon Silverthorne. After a further year at the Ontario Hospital in Orillia he proceeded to England where he spent one year at St. Bartholomew's Hospital in London. On his return to Toronto he was appointed to the visiting staff of St. Michael's Hospital where he was associated again for a short time with Dr. Silverthorne. In 1915 he was invited to join the staff of the Toronto General Hospital where he formed an association with Dr. F. N. G. Starr which lasted until the latter's death in 1934. Shortly after coming to the General Hospital

he proceeded overseas with the Canadian Army Medical Corps where he served with No. 4 Canadian General Hospital. On his return to Canada he resumed his connection with the Toronto General Hospital and the University of Toronto.

Very early in his career Dr. Graham gave great promise as a teacher. Many who came under his influence in those early days recall with pleasure his enthusiasm, his pleasing personality, his evident desire to be helpful, and his thoroughness. These were the qualities which, along with the mastery of the subject of surgery which he acquired with the years, made him one of the greatest surgical teachers of our time. He was much in demand as a speaker before surgical societies in this country and the United States. A year ago he addressed the Mexican Academy of Surgery and at the time of his death had been invited to deliver the Martin lecture before the American College of Surgeons.

He contributed many articles to the surgical journals of Great Britain, the United States and Canada. In later years these had been devoted largely to abdominal surgery which had come to be his special field and in which he had become a master. Of particular interest to University of Toronto students is the fact that he was the first to remove from the pancreas an adenoma of the Islets of Langerhans.

He was a Fellow of the Royal College of Surgeons of Canada and a member of council, a Fellow of the American College of Surgeons, a Fellow of the Mexican Academy of Surgery, a member of the American Surgical Association and the Central Surgical Association, a Fellow of the Detroit Academy of Surgery and President of the Canadian Society of Clinical Surgeons.

Despite an unusually busy professional life he found time for many non-professional interests. He was fond of music, was a skilled amateur photographer, enjoyed golfing, hunting, fishing and sailing. He was devoted to his summer home in Muskoka.

Dr. Graham's death is a great loss to the University and to the community. Those who knew him best take solace in the knowledge that it is the kind of end he would have wished. He could not bear the thought of inactivity.

He is survived by his widow, the former Beatrice Barry, one son, Barry, a daughter, Mrs. Peter Allen and a sister, Miss Ella, of London, Ontario.

Robert M. Janes
Professor or Surgery

INTERCELLULAR SUBSTANCES

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INTRODUCTION

Intercellular substances, although involved in many disease processes, have not been investigated until recently with the same vigour as have cells. In the past few years, however, much new information has been obtained about them: their chemistry has been further elucidated, and biological mechanisms which alter the physical state of some of them have been discovered. It is evident that these non-living materials are not as inert as was generally supposed. Although it is too soon to assess the significance of the newer findings, it seems not unlikely that they and the further investigations they will inspire, will lead to a better understanding of the pathogenesis of at least some of those diseases in which intercellular substances are profoundly affected. In any event intercellular substances are sufficiently important, and the recent advances in knowledge about them sufficiently interesting, to justify at this time a survey of what is known about them.

TYPES OF INTERCELLULAR SUBSTANCE

Classified morphologically there are two general kinds of intercellular substances present in the body: a kind that is present in the form of fibres, which we shall term the *formed* type, and a kind that is present in the form of jellies, which we shall term the *amorphous* type. Both formed and amorphous types are present in most of the sites in the body occupied by intercellular substances.

(1) *Formed Type*

The formed intercellular substances are present in the body as three kinds of fibres termed the reticular, collagenic and elastic fibres. They are all proteins of the albuminoid type, i.e., they are insoluble in neutral solvents and hence they are resistant to chemical change; indeed certain kinds of the formed intercellular substances have been found preserved in the skin and blood vessels of Egyptian mummies (1).

(a) *Reticular Fibres*

These are delicate strands of material, one to two micra in width, which are found in loose connective tissue, and also in organs where delicate support for cells is required (e.g., spleen). They stain faintly or not at all with haemotoxylin and eosin, but can be demonstrated easily by silver impregnation. Because of their affinity for silver, they are sometimes called *argyrophilic* fibres.

(b) *Collagenic Fibres*

Collagenic fibres consist of larger fibres, (thirty or more micra in width) made up of many closely applied fibrils. For this reason they commonly possess a fibrillated appearance. Collagenic fibres are found in loose connective

tissue where support stronger than that provided by reticular fibres is needed, and also in ligaments, tendons, fascia, and other sites where considerable tensile strength is required. Although collagenic fibres stain red with haemotoxylin and eosin, they are better demonstrated by one of the stains more or less specific for them such as Van Gieson's or Mallory's triple stain.

Both collagenic and reticular fibres are made up of collagenic *fibrils* held together with a *cement substance.* The number of fibrils present in a fibre determines whether it is to be called a collagenic or a reticular fibre: the former may contain a hundred or more fibrils, the latter but two or three. Recent studies of these fibrils with the electron microscope indicate that they may be further split into submicroscopic *protofibrils,* and that both fibrils and protofibrils possess regularly arranged cross-striations (2).

(c) *Elastic Fibres*

Intermediate in size between collagenic and reticular fibres, elastic fibres are characteristically branched, a feature which helps to distinguish them from collagenic fibres. They consist of the albuminoid elastin, and are homogeneous rather than fibrillar. They are the most resistant of the three types of fibres to chemical change. Elastic fibres are found in the walls of larger blood vessels, in elastic cartilage, in certain ligaments, and in loose connective tissue. Although they may stain red with haemotoxylin and eosin, they can be demonstrated more readily with specific stains such as Weigert's elastic tissue stain.

(2) *Amorphous Types*

The amorphous intercellular substances may be imperfectly classified on morphological grounds into two main types: ground substance and cement substance. The amorphous jelly that is found filling the spaces between the fibres of loose connective tissue is an example of a ground substance, while the material that binds together the fibrils within a collagenic fibre is an example of a cement substance. Both ground substance and cement substance belong to a class of chemical materials to which Meyer (3) has given the name *mucopolysaccharides.* The materials now known as mucopolysaccharides were formerly included as mucins and mucoids in the group of glycoproteins. They are highly polymerized polysaccharides containing hexosamine as one component and occurring in nature either free or as protein salts. Their high degree of polymerization causes them to form colloidal systems of various degrees of rigidity. The mucopolysaccharides are found in association with a protein, the nature of which is unknown, but which is distinct from the protein of the formed types of intercellular substances.

The two types of mucopolysaccharides found in mammals may be distinguished from each other by whether or not they contain sulphuric acid.

(a) *Non-sulphuric acid-containing-mucopolysaccharides*

The only example of this type found in the body has been named *hyaluronic acid.* It is the principal constituent of the ground substance of connective tissue. Its high degree of polymerization accounts for the jelly-like

quality of the ground substance. On hydrolysis, hyaluronic acid yields equimolecular parts of acetyl glucosamine and glucuronic acid (4). It is readily soluble in water, and when dilute acetic acid is added to a solution of it an opaque pellicle, called a *mucin clot,* is formed. The mucin clot forms only when the hyaluronic acid is highly polymerized, therefore the amount of clot formed may be used as a rough guide to the degree of polymerization.

Hyaluronic acid has been recovered from whole skin, Wharton's jelly, the aqueous and vitreous humours of the eye, and synovial fluid (5). It has also been recovered from exudates of mesodermal tumours: synovialomas, and mesotheliomas of pleura and peritoneum (5). It accounts for such jelly-like qualities as these substances possess.

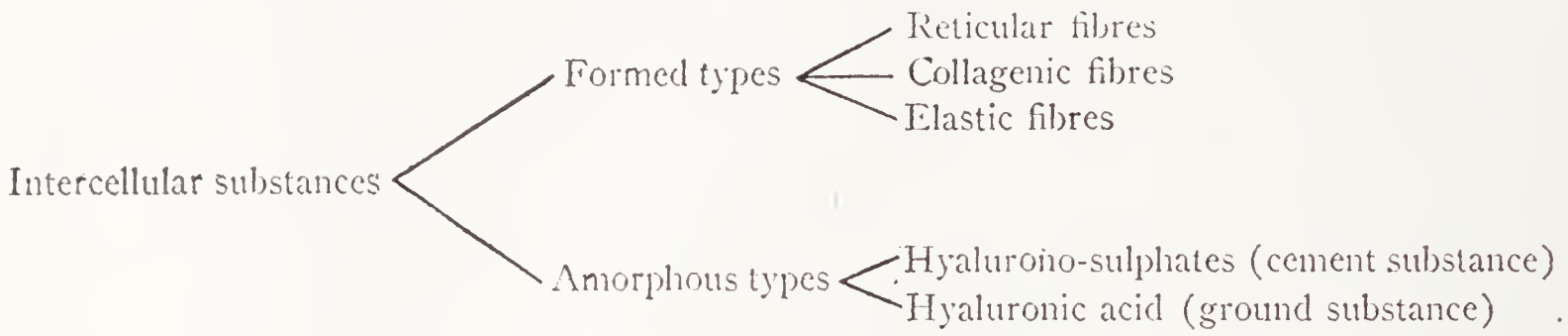
(b) *Sulphuric Acid-containing-mucopolysaccharides*

This type of mucopolysaccharide differs from hyaluronic acid by possessing a sulphuric acid radicle on the hexosamine part of its molecule. For this reason the sulphuric acid-containing-mucopolysaccharides are sometimes referred to as hyalurono-sulphates. The hyalurono-sulphates enter into firm chemical union with the unknown protein associated with the mucopolysaccharides. This union is partly a true salt linkage, for the acid keto and sulphuric groups of the mucopolysaccharide are linked to the basic amino groups of the protein (6). The hyalurono-sulphates are insoluble in water because of their union with the protein; it is probable that in the body they form stiff gels of a rather permanent nature.

It has already been mentioned that the cement substance about collagenic fibrils is a typical example of a sulphuric acid-containing-mucopolysaccharide. In cartilage, this type of mucopolysaccharide is more familiarly known as *chondroitin sulphuric acid.* Chondroitin sulphuric acid is a highly specialized form of cement substance, for it is found surrounding a dense network of collagenic fibrils in the intercellular substance of cartilage. The presence of these fibrils is masked in ordinary preparations because their refractive index is similar to that of chondroitin sulphuric acid. They may be demonstrated with suitable stains, but to better advantage after the chondroitin sulphuric acid has been removed from the cartilage (7). In cartilage, chondroitin sulphuric acid is salt-linked directly with collagen, for the unknown protein which appears in other locations does not seem to be present (8). It is true that some protein is obtained during the extraction of chondroitin sulphuric acid from cartilage; this is thought to be a soluble form of collagen (8).

In general, the hyalurono-sulphates are the chief constituent of the cement substance of all connective tissue, even when the connective tissue is highly specialized. They have been recovered from cornea, whole skin, Wharton's jelly, tendon, fascia, cartilage and gastric mucosa (9).The hyalurono-sulphate of gastric mucosa is found in its mucous secretion. Since its origin here is epithelial, an exception is provided to the rule that this type of mucopolysaccharide is found in connective tissue alone.

The following plan provides a helpful summary of the types of intercellular substances. In general, they consist of combinations of protein fibres, surrounded with cement substance, and embedded in a jelly-like ground substance.



The proportion of each type varies in different tissues: at one extreme is Wharton's jelly, which consists almost entirely of mucopolysaccharides, with few or no fibres, while at the other extreme is tendon, which consists almost entirely of fibres whose fibrils are bound together with thin films of cement substance. Ordinary loose connective tissue lies mid-way between these extremes, for it contains approximately equal parts of both the formed and amorphous types of intercellular substances.

THE STAINING PROPERTIES OF INTERCELLULAR SUBSTANCES

The fibrous types may be stained by several well known procedures already briefly mentioned. A detailed description of these methods may be found in any reference book on histological technique.

The methods for staining the amorphous types are not so well established. Hyaluronic acid is difficult to stain, largely because it dissolves away in ordinary aqueous fixatives. Even after tissue containing it is fixed in alcohol, in which it is insoluble, it is still difficult to identify because no stains are known which will colour it specifically. Nevertheless, two indirect methods for its identification have been described. Hale's method (10) depends on the great affinity hyaluronic acid has for heavy metals. A suitable heavy metal, after precipitation by the hyaluronic acid present in the section being stained, may then be identified by any colour-producing reaction for that metal, e.g., iron by the Prussian blue reaction. The method described by McManus (11) takes advantage of the fact that aldehyde groups are produced on hyaluronic acid by gentle hydrolysis with weak acids. These aldehyde groups may be identified by the red colour they produce with Schiff's reagent (fuchsin-sulphurous acid.)

The hyalurono-sulphates may be demonstrated more easily than hyaluronic acid because they are insoluble in water and hence are not washed out by aqueous fixatives. Furthermore they stain metachromatically with certain dyes. Metachromasia occurs in those dyes which possess dilution shift, i.e., on dilution of the dye, its colour shifts to another region of the spectrum. This phenomenon is thought to be due to a change in the angle between the nitrogen bonds in the dye (12). On dilution of the dye, the angle between these bonds increases, causing expansion of the dye molecule; this expanded molecule transmits a different wave

length of light and thus possesses a different colour. Toluidene blue is a typical dye demonstrating dilution shift. In concentrated solutions it is deep red-violet in colour, while in dilute solutions it is sky-blue. When tissue is stained with dilute toluidene blue, the hyalurono-sulphates, which are metachromatic, become red-violet in colour, whereas the non-metachromatic elements are coloured blue. This metachromasia is believed to be the result of the dye molecule combining with the sulphuric acid groups of the hyalurono-sulphates. Metachromasia, however, is not confined to the sulphuric acid-containing-mucopolysaccharides. Bensley (13) points out that a variety of substances exhibit metachromasia, and Meyer (5) states that hyaluronic acid is also metachromatic, but that it only manifests this property in concentrations far above those found in vivo.

HEPARIN

Heparin is a sulphuric acid-containing-mucopolysaccharide similar in structure to chondroitin sulphuric acid (14). It exhibits a high degree of metachromasia when stained with dilute toluidene blue. The granules of mast cells, connective tissue cells commonly found adjacent to capillaries, are also metachromatic. Wilander (15) demonstrated that the heparin content of various organs and tissues bore a direct relationship to their mast cell count. Oliver et al (16) recently found that spontaneous mast cell tumours of dogs contain large amounts of heparin. These observations strongly suggest that the metachromatic granules of mast cells are the source of the heparin obtained on extracting various tissues.

ENZYMES AFFECTING THE INTERCELLULAR SUBSTANCES

Recently much interest has developed concerning certain enzymes, obtained from bacteria and other sources, which profoundly affect the physical state of the amorphous types of intercellular substances. It is convenient to present the information about these enzymes in historical sequence, for as so often happens in the development of new knowledge, some confusion of nomenclature has occurred.

In 1929, Duran Reynals first reported (17) that simple aqueous extracts of mammalian testicle, when injected intradermally, spread over a wide area, instead of forming a sharply circumscribed bleb as a control injection (e.g., of saline) would do. This effect may be more strikingly demonstrated by adding a colloidal dye (india ink or trypan blue) to the injection (fig. I.) This phenomenon was termed "spreading" by Duran Reynals, and he postulated that mammalian testicle contained a "spreading factor". Similar spreading factors were subsequently discovered in leach extracts, bee and wasp stings, and certain snake venoms (18). For many years the nature of the spreading phenomenon remained unknown, as histological sections made of the site of injection revealed no structural changes in the skin.

In 1936, Meyer, who had established the chemical nature of hyaluronic acid, discovered an enzyme which he named *hyaluronidase,* capable of depolymerizing the hyaluronic acid molecule (19). This enzyme was recovered from the filtrates of broth cultures of pneumococci, certain forms of streptococci, and staphylococci. As the viscosity of hyaluronic acid solutions is due to the high degree of polymeri-

zation of the hyaluronic acid, it can be readily appreciated that the effect of hyaluronidase is to decrease the viscosity of such solutions. The degree of reduction in viscosity produced by hyaluronidase is proportional to the degree of depolymerization of the hyaluronic acid molecule.

In 1939, Chain and Duthie (20) discovered that extracts of testicle containing the spreading factor of Duran Reynals are capable of reducing the viscosity of synovial fluid. As it was already known that synovial fluid owes its high viscosity to hyaluronic acid, Chain and Duthie concluded that testicle extracts were capable

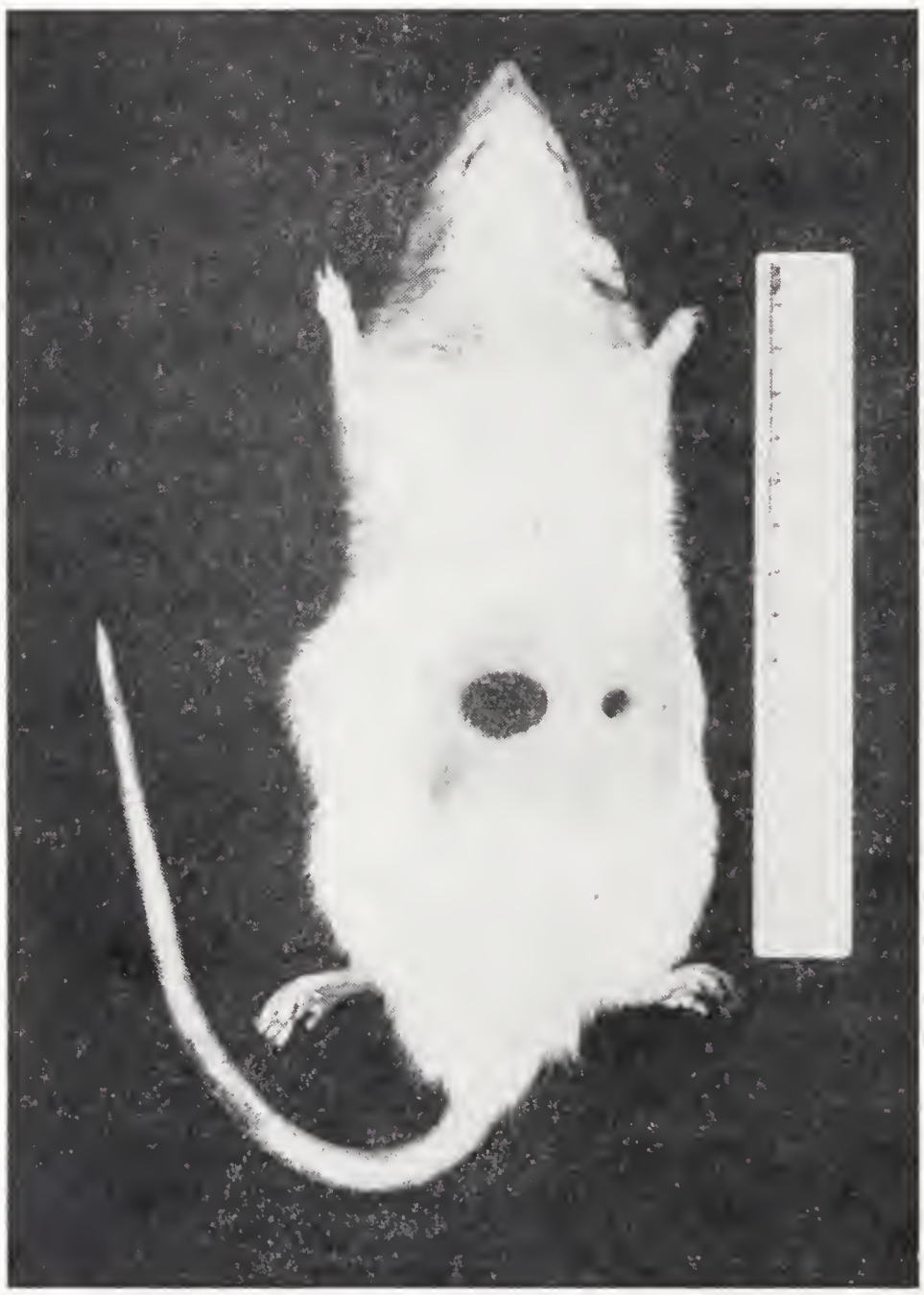


Fig. 1. Spreading phenomenon of Duran Reynals.

Large wheal: intradermal injection of 1/10 cc. of a mixture of equal parts of aqueous extract of rat testicle and india ink. Small wheal: control injection of 1/10 cc. of a mixture of equal parts of saline and india ink.

of depolymerizing this hyaluronic acid, i.e., they contained hyaluronidase. Very quickly it was proven that testicle extract did indeed contain hyaluronidase, and conversely that preparations of hyaluronidase were capable of producing spreading (21). Further experiments revealed that although all forms of hyaluronidase are capable of producing spreading, not all spreading factors contain hyaluronidase.

This has led Duran Reynals (22) to classify the spreading factors into two groups: (a) those which contain hyaluronidase, and (b) those which do not contain hyaluronidase.

Although most hyaluronidases are capable of depolymerizing hyaluronic acid only, certain preparations made from testicle extract wil also depolymerize chondroitin sulphuric acid and certain other hyalurono-sulphates (23). As this reaction has a different pH optimum, and requires a much longer time to occur than the reaction of hyaluronidase with hyaluronic acid, Meyer (5) has suggested that testicle extracts contain two enzymes; one is hyaluronidase, and the other an enzyme capable of depolymerizing the sulphuric acid-containing-mucopolysaccharides.

The fact that testicle extracts contain hyaluronidase suggests an explanation for the spreading phenomenon: the enzyme depolymerizes the hyaluronic acid in the ground substance (and possibly also the hyalurono-sulphates in the cement substance), with an accompanying decrease in their viscosity. This decrease in viscosity enables injected fluids or dyes to spread over a wide area, and thus prevents wheal formation. The presence of the enzyme in testicle extracts also provides an interesting example of a possible physiological rôle. When an ovum leaves the ovary, it is surrounded with a layer of follicular cells which, by preventing contact with spermatozoa, effectively prevent fertilization. Leonard et al (24) have shown that the hyaluronidase present in semen depolymerizes the cement substance between these follicular cells so that they disperse, and leave the ovum exposed for fertilization.

THE EFFECTS OF HYALURONIDASE IN TISSUES

(a) *In Vitro*

Although nearly all of the experimental data concerning the effects of hyaluronidase have been obtained from experiments in which purified extracts of the mucopolysaccharides were used, a few reports are available concerning the effect of the enzyme on whole tissue. Wislocki et al (25) report that hyaluronidase prevents Wharton's jelly, vitreous humour, synovial fluid, nucleus pulposus, ovarian follicular fluid, skin, and the connective tissue component of several different mucous membranes from staining metachromatically with toluidene blue. Although they used testicular hyaluronidase, their particular preparation had no effect on cartilage. Using a different preparation of testicular hyaluronidase, the author has found that cartilage slices exhibit some loss of metachromasia, and that this presumed loss of chondroitin sulphuric acid from the slices unmasks the collagenic fibrils they contain.

(b) *In Vivo*

The in vivo effects of hyaluronidase are difficult to determine, because it has not yet been possible to obtain a pure preparation of the enzyme. Duran Reynals (26) has reported that intravenously injected testicle extract produces increased capillary permeability, but Meyer (7) believes that this effect is due to the high histamine content of the relatively impure preparations used. Meyer has found

(5) that the enzyme has no effect on capillary permeability, that it disappears from the blood stream within half an hour after intravenous injection, and also (8) that it is not antigenic in experimental animals.

HAS HYALURONIDASE A PHYSIOLOGICAL RÔLE?

Mention has already been made of the possible rôle of hyaluronidase in fertilization.

Meyer and others (23) have demonstrated that hyaluronidase is present in the ciliary body of the eye, and also in the skin, where it appears in an inactive form. (It is likely that it occurs in the mesodermal elements of whole skin (8).) The presence of the enzyme in this latter location suggests the possibility of it playing a part in the maintenance of fluid balance in the tissues, for by changing the degree of polymerization of hyaluronic acid, it could affect the ability of the ground substance to hold water and also the rate at which tissue fluid and dissolved metabolites circulate through it.

THE FORMATION OF INTERCELLULAR SUBSTANCES

Wound Healing—New intercellular substances are produced in the healing of wounds. During the stage of fibroblastic proliferation in a wound, the intercellular substance that forms first is deeply metachromatic but devoid of fibres. This is soon followed by the appearance of many collagenic fibrils bound together into fibres by metachromatic cement substance. A similar course of events was described by Bensley (13) in the connective tissue of the guinea pig pancreas following ligation of the pancreatic duct. The aging of connective tissue, therefore, is characterized by the appearance of fibres. Meyer (5) has advanced an interesting theory to explain the formation of these components. Undifferentiated mesenchymal cells (such as are found in Wharton's jelly or in the early repair of a wound) are capable of secreting a gelatin, which is the precursor of collagen, and both hyaluronic acid and hyalurono-sulphates. Because these mucopolysaccharides are acid in quality, they tend to denature the collagen precursor, and, Meyer suggests, precipitate it in the form of fibrils which may be recognized under the microscope as the fibrils in reticular and collagenic fibres. The sulphuric acid-containing-mucopolysaccharides, presumably because of their high electrostatic charge, have a greater affinity for protein than hyaluronic acid, and hence become concentrated about the collagenic fibres as the cement substance.

Sylven (30) has observed that the regional mast cells disappear following a wound. This he relates to the appearance of the metachromatic ground substance in the repair process. Subsequently, as the fibrous scar tissue is formed, the mast cell re-appear in large numbers. Sylven concludes that the mast cell granules represent a reserve supply of sulphuric acid—containing-mucopolysaccharides that are released when there is need for the formation of new connective tissue. When the fibres have been laid down, excess hyalurono-sulphates are, he thinks, again taken up by the mast cells.

The effect of Endocrines—It has been demonstrated that there is an increase in the mucopolysaccharide content of the sexual skin of monkeys during oestrus

(27). Anterior pituitary luteinizing hormone (prolan B) causes an increase in the spreading reaction in the skin of treated animals (28). These findings were foreseen by Bensley (13) who demonstrated that during the premenstrual phase there was an increase in the non-metachromatically staining ground substance of the endometrium, and that this was followed by the appearance of metachromatically staining ground substance during the stage of repair. Injections of testosterone restore metachromasia to the comb of a capon.

Rôle of Vitamin C—Wolbach (29) demonstrated that in vitamin C deficiency, wound healing was characterized by failure of fibre formation, and that the administration of vitamin C restored fibre formation to normal. Meyer (5) suggests that ascorbic acid (a hexose acid) may actually be a component of the hyaluronosulphate of the cement substance, and that when cement substance formation is deficient, so also will be fibre formation. It is also possible that lack of ascorbic acid results in an impaired maintenance of the cement substance between the endothelial cells of capillaries, and so accounts for the characteristic haemorrhages of scurvy.

It is interesting to note that adult tissues containing fairly large amounts of sulphuric acid-containing-mucopolysaccharides, notably cartilage and cornea, are non-vascular. Scar formation in a wound is accompanied by decrease in vascularity. Wislocki et al (25) have pointed out that human umbilical cord, which possesses a rich capillary bed, is but faintly metachromatic, whereas pig umbilical cord, which contains few capillaries, is deeply metachromatic. It seems reasonable to associate the formation of sulphuric acid-containing-mucopolysaccharides with lack of vascularity. It may be that the rigid gels formed by these types of mucopolysaccharides are of such a nature that they partly compensate for the loss of blood supply, for substances dissolved in tissue fluids could rapidly diffuse through the water bound in the fibrillae of these gels.

SOME POSSIBLE RELATIONSHIPS TO DISEASED STATES

(1) *Glaucoma*

In a previous paragraph it was suggested that the hyaluronidase content of certain connective tissues might play a part in controlling their water balance. It is interesting to speculate whether this is true in the eye. The hyaluronic acid of the aqueous humour is normally 95% depolymerized, presumably by the hyaluronidase produced in the ciliary body (5). It can be visualized that either increased hyaluronic acid production or decreased hyaluronidase production would lead to increase in the viscosity of the aqueous humour, with resultant retardation of its absorption and, therefore, increased intra-ocular pressure. It remains to be proven whether or not the hyaluronic acid of the aqueous humour is more highly polymerized in acute glaucoma than in the normal eye.

(2) *Pre-Tibial Myxoedema*

In some cases of toxic goitre, there is swelling of the skin over the shins, a condition which is sometimes referred to as "pre-tibial myxoedema." It has been

reported that the affected skin in this condition contains an increased amount of mucopolysaccharides (31).

(3) *Amyloid Disease*

Amyloid is a mucopolysaccharide which Meyer states (5) is an abnormal form of heparin. This brings up interesting possibilities which have not yet been investigated.

(4) *Inflammatory Conditions*

(a) *Bacterial Virulence*

The original discovery of hyaluronidase in filtrates of bacteria, followed by the discovery that it produces spreading, has lead to many experiments in an attempt to relate the virulence of bacteria to their ability to secrete hyaluronidase. Much of this work has been recently reviewed by Duran Reynals (22). It is concluded that there is no direct relationship between the virulence of bacteria and their ability to produce hyaluronidase; one reason for this appears to be that at least some hyaluronidase-producing bacteria spread so widely in the intercellular substances that they are readily phagocytosed.

(b) *Arthritis*

The recent observation of Guerra (32) that hyaluronidase fails to spread in the skin of patients receiving salicylates has stimulated much interest in the possible rôle of hyaluronidase in the pathogenesis of rheumatic fever. Guerra felt that hyaluronidase excess may be a factor in this condition, and that salicylates act as specific inhibitors of the enzyme. It has subsequently been shown by Meyer (5) that salicylates in high concentration have no inhibitory effect on the enzyme in vitro; it is suggested that their effect may be on intercellular substances rather than on the enzyme.

Guerra's observations were followed by those of Ragan (33) who pointed out that the synovial fluid in many forms of arthritis (including the persistant synovial effusion following simple trauma) is commonly reduced in viscosity, and also that it fails to form a mucin clot with the addition of dilute acetic acid. Both these effects can be produced in normal synovial fluid by the addition of hyaluronidase, but in spite of this, efforts to recover hyaluronidase from pathological joint fluids, and synovial membranes (both by extraction of fresh material and by tissue cultures) have been unsuccessful (7).

A common feature of the cartilage lesion in several forms of arthritis is loss of metachromasia; the surface of the cartilage tends to become fibrillated and to undergo a fibrous metaplasia. Although the author has produced a somewhat similar fibrillation by incubating cartilage slices in hyaluronidase, there is as yet no substantial evidence to indicate that excess of hyaluronidase is a factor in producing the cartilaginous lesions found in joint diseases.

It has already been mentioned that the formation of the sulphuric acid-containing-mucopolysaccharides seems to be associated with decrease in vascularity. The presence of a vascular pannus in some forms of arthritis could, then, inhibit

the formation of chondroitin sulphuric acid by chondrocytes, so that they would produce instead a fibrous tissue containing many collagenic fibres.

(c) *Fibrinoid Degeneration*

Much interest has centered about the nature of the lesion described as "fibrinoid degeneration". This lesion is characterized (34) in its early stgaes by a swelling of the cement substance about the collagenic fibrils in connective tissue, so that the individual fibrils become granular and finally degenerate into an amorphous material, which because it possesses the morphological and staining characteristics of fibrin is termed "fibrinoid" degeneration. The final stage is characterized by invasion of the area by the cells characteristic of chronic inflammation and often by giant cells. Commonly there is an accompanying fibrosis in the adjacent tissue, and this new fibrous tissue may in turn undergo fibrinoid degeneration.

Fibrinoid degeneration is found in the Aschoff nodules of rheumatic fever, in the skin nodules of rheumatoid arthritis, in the skin in scleroderma, in the intima and media of medium-sized arteries in peri-arteritis nodosa, and sometimes in the splenic vessels in allergy (34). The similarity of the lesion in each of these diseases hints that they have a common etiology; it has been suggested that the lesion represents an allergic response of connective tissue. The early lesion (swelling of the cement substance) could theoretically be produced by hyaluronidase, but in the author's hands attempts to produce such a lesion experimentally have not been very successful. Although the lesion is referred to as a degeneration, it is possible that at least in part it is due to faulty production of fibrils by fibroblasts.

(5) *Pharmocological Uses of Hyaluronidase*

(a) *Sterility*

The fact that hyaluronidase is present in testicle, and is presumably necessary for the fertilization of ova, has led to its use in the treatment of certain forms of sterility. Successful results have been claimed in cases where the hyaluronidase content of semen is low (35).

(b) *Aspiration of Mucoid Secretions*

Hyaluronidase has been injected into the knee joints of patients with rheumatoid arthritis (5); this procedure has resulted in a marked reduction of the viscosity of the synovial fluid, but no change was observed in the underlying disease. The enzyme has also been used to reduce the viscosity of pleural fluid in a patient suffering from mesenthelioma of the pleura. This fluid was of a honey-like consistency, but after treatment with hyaluronidase its viscosity was greatly reduced, so that it could be aspirated readily.

(c) *Hypodermoclysis*

Hyaluronidase has been added to hypodermically administered fluids to facilitate their absorption and to prevent painful distension of the subcutaneous tissues. It is reported to be particularly effective in administering interstitial fluids to infants (36)

The author wishes to acknowledge with gratitude the kind advice and criticism of Professor Arthur W. Ham in the preparation of this article.

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THE LABORATORY DIAGNOSIS OF SUPERFICIAL FUNGOUS INFECTIONS

RAYMOND C. SMITH, B.A., M.D.

Medical mycology is now recognized as a science of importance and interest to all physicians. In the past only a few specialists have been familiar with the difficult classification and involved terminology of the subject. Recently these deterrents have been simplified and it is now possible for the mycologist or pathologist to identify any pathogenic fungus present in infected tissue and report the findings in a manner which is intelligible to the practising doctor. Only during the recent war did the importance of mycotic disease in the differential diagnosis of practically every obscure infection become recognized. The development of relatively specific fungicidal therapeutic agents has emphasized the need for exact and detailed indentification of the causative organism, since the treatment of choice will be modified by this information. Depending on the species of the fungus, the physician will know that the infection will be refractory to treatment, requiring prolonged and careful management, or that it will respond quickly to simple, non-specific therapy.

Fungi are microscopic members of the plant kingdom but have no definite roots, stems or leaves. Since they do not contain chlorophyll they are parasitic or saprophytic and derive energy for growth from the organic material in which they live. These micro-organisms may be one-celled, as the yeasts, or multicellular, composed of spores and elongated cells joined end-to-end to form filaments or hyphae. The spores are for reproduction or for maintenance of the organism during adverse conditions. The hyphae are vegetative in function.

The ringworm fungi reproduce by asexual spores which are termed conidia. In different species these cells vary in size, shape, the character of the wall, the number of septations and the manner in which they are borne on the hyphae.

Large spores are termed *"macroconidia"* or *"fuseaux"* and occur singly or in clumps on the end of a hyphal filament. These conidia are oat-shaped and are multiseptate.

Small spores or *"microconidia"* are pear-shaped and occur singly or in grape-like clusters along a hypha or its branches.

"Arthrospores" are formed under certain conditions of growth when the protoplasm of a hypha fragments into a chain of cuboidal spores.

"Chlamydospores" are thick-walled, resting cells which occur in the hyphal threads or at the ends of the filaments of some species.

In tissues the vegetative filamentous form of the fungus is usually found but in older lesions spores may also be present. The yeast-like fungi are seen in tissues as budding oval cells alone or interspersed with pseudohyphae. On artificial cultural media the hyphae of the ringworm fungi sometimes occur in unusual forms which are characteristic of the species and useful in identifying the organism.

"Racquet hyphae" are formed by the ballooning of the growing ends of the filaments.

"Nodular organs" are formed by the hyphae twisting about one another or intertwining.

A *"pectinate body"* looks like a broken comb and is formed by a series of short projections along one side of a hypha.

"Spiral hyphae" are seen when the filaments occur in coil-like forms.

"Favic chandeliers" are formed by hyphae which branch in such a manner that the configuration is similar to the shape of a reindeer horn.

All fungi which are pathogenic for humans are members of the sub-class *"Fungi imperfecti"*. Four species are responsible for the superficial types of infection. These are *"Microsporum"*, *"Trichophyton"* and *"Epidermophyton"* (all of the genus *"Dermatophyta"*)and *"Candida"* (*Monilia*) *albicans"* (of the genus *"Pseudosaccharomycetaceae"*). These organisms do not invade the skin deeper than the superficial layers of the epidermis. Other genera and species cause systemic infections and produce a different type of pathological reaction in the skin if it is involved.

When clinical symptoms and signs suggest that a fungus is the causative agent in an infection of the skin, nails or scalp, several laboratory procedures are available for the isolation and identification of any micro-organism present. The most important of these are direct microscopic examination of infected tissues, and culture of this material on special media. Animal inoculation, agglutination and fermentation tests, precipitation and complement fixation tests and histological examination of the infected tissue are seldom necessary to establish a diagnosis. In a large proportion of cases either direct examination or culture is positive but negative results, even when repeated, do not necessarily rule out a fungus as the responsible agent.

Collection of Infected Material

Scales, macerated skin, pieces of nail, hair and roofs of vesicles and bullae may be removed from early lesions, preferably from untreated areas, for examination and culture. A small specimen from each type of lesion should be secured. A higher percentage of positive results will be found if the tissue is scraped from the active border of a lesion rather than from the central macerated or bullous area.

Examination of the scalp under a Wood's lamp will indicate the infected hairs which should be cultured. Direct microscopic examination of typical fluorescent hairs (Wood's lamp) in cases of ringworm of the scalp is unnecessary since fluorescence occurs only when spores are present. Fragments of the deeper or crumbly portions of a nail should be selected for examination.

The area from which the specimen is to be removed must be thoroughly cleansed with 70% alcohol to remove most of the contaminating saprophytic fungi and bacteria.

The equipment necessary for the collection of specimens is simple A dull

scalpel, sharp-pointed scissors, nail clippers and depilatory forceps will suffice. These should be disinfected in 10% cresol for half an hour following use and then rinsed in water and 70% alcohol. The material removed is placed on a microscopic slide for direct examination and in a sterile container or directly on media for culture.

Direct Microscopic Examination

Microscopic examination of infected tissue is often sufficient to establish a diagnosis but does not identify the species of the fungus. The relative frequency in scales of filamentous and spore forms or the position of spores inside or outside the hair is sometimes suggestive, but not diagnostic, of certain species.

The specimen is placed in a drop of 20% potassium hydroxide solution on a clean microscopic slide and a cover slip applied. The preparation should be warmed gently for several minutes to clear the cells. Microscopic examination with subdued light will usually demonstrate filament or spore forms if they are present. If these are not found, repeated application of potassium hydroxide and warming may be necessary to reveal the organism.

In infected hair hyphal forms are rarely seen and the spores vary considerably in size. In *"Microsporum"* infections small spores are seen in a mosaic sheath outside the hair. In hairs infected with *"Trichophyton"* the spores are larger and are present either inside the hair (endothrix type) or on the surface of the hair (ectothrix type). Usually endothrix spores are present in a linear arrangement while the ectothrix forms are somewhat smaller and arranged irregularly in groups. In infected scales from early lesions the filamentous form of the fungus predominates but if the specimen has been removed from a vesicle or from a macerated area, chains of spores are most commonly found. Both hyphal and spore forms are present in nail specimens. *"Candida albicans"* occurs in skin or nails as budding yeast-like cells with or without hyphal forms.

Several artefacts often cause confusion but once the appearance of these is known they are easily recognized in future examinations. The "mosaic fungus" has the appearance of filaments in a pavement-like arrangement. The origin of this artefact is obscure but it is generally considered to be due to the presence of some refractile substance (cholesterol?) between the epithelial cells. Saprophytic fungous forms are usually seen in large numbers when they are present. They occur in specimens from old lesions and appear in the microscopic preparation as large segments and often have a green or brown tone. Oil, grease, air bubbles, hair and fibres of wool and cotton must be differentiated from spores and filamentous forms.

Culture of Infected Material

To determine the species of the infecting fungus it is necessary to study its appearance and behaviour during growth on artificial media. For routine cultures Sabouraud's dextrose agar (1% peptone, 2% agar, 4% crude dextrose, pH 5.6-5.8) is used. To this is added penicillin and streptomycin in concentrations of 100 units of each per c.c. of medium to suppress the growth of contaminating bacteria.

TABLE I

CHARACTERISTICS OF FUNGI IN TISSUE AND ON CULTURE

Organism	Tissues Affected	Microscopic Features in Tissues	Cultural Characteristics	Culture Mount			
				Special Hyphae	Fuseaux	Micro-conidia	Chlamydo-spores
EPIDERMOPHYTON *E. floccosum*	Skin; nails rarely.	Many filaments; arthrospores.	Slow-growing, olive to green in colour, scanty aerial hyphae. Early pleomorphism. No pigment in medium.	None.	*Clusters of smooth, thin-walled spores with rounded ends, 2-5 cells.*	None.	In vegetative hyphae in medium.
MICROSPORUM *M. canis*	Scalp (children). Skin and nails.	Mosaic sheath of small arthrospores (ectothrix). Sparse filaments and occasional arthrospores.	Abundant woolly aerial growth, white to buff in colour. *Yellow pigment in medium.*	None.	*Many; large; thick, rough walls, ending in points. 8-15 cells.*	Singly.	None.
M. audouini	Scalp (children). Skin and nails.	(As for *M. canis.*) Filaments and occasional arthrospores.	Slower-growing, greyish-white to buff, downy, scant aerial growth. Red-brown pigment in substrate.	*Pectinate hyphae.*	Few; thick, rough walls; pointed; few cells.	Singly.	*Frequent.*
M. gypseum	Scalp (children). Skin.	(As for *M. canis.*) Filaments and arthrospores.	Fast-growing, white to buff, powdery. Early pleomorphism. No pigment in medium.	None.	Many; thick-walled; blunt ends; finely roughened surface.	Singly or in clusters.	None.
TRICHOPHYTON Rubrum Group (*T. rubrum*)	Skin and nails. Hair rarely.	Filaments and arthrospores. Ectothrix, large spores.	White to red, downy or dry, often cracked. *Red pigment in medium.*	None.	Few; thin, parallel smooth walls; rounded ends.	Singly or in clusters.	Occasionally.

TABLE I—*Continued*

Gypseum Group (*T. mentagrophytes*)	Skin and nails. Hair rarely.	Branching, septate hyphae. Arthrospores in chains. Ectothrix, large spores.	Powdery or fluffy and white, early; later, buff and flat. Tan pigment in medium.	*Numerous spiral hyphae.*	Few; thin-walled; smooth; constricted at septa; blunt ends.	*Numerous: singly or in clusters.*	Occasionally.
Crateriform Group (*T. tonsurans*)	Skin and nails. Hair rarely.	Filaments and arthrospores. Endothrix, large spores.	*Folded; central crater;* powdery or velvety; white; slow-growing. No pigment.	Racquet hyphae occasionally.	Rarely seen: clavate; thin-walled.	Numerous; singly.	Occasionally.
Rosaceum Group (*T. rosaceum*)	Skin and nails. Hair rarely.	Branching filaments, arthrospores. Ectothrix, large spores.	Small, downy colonies, white to rose in colour. Rose or violet pigment in medium.	Racquet hyphae.	*None.*	Common: singly.	*Common.*
Faviform Group (*T. schoenleini*)	Skin and nails. Hair.	Sparse filaments. Endothrix, *large spores in chains.*	Slow-growing, *smooth, waxy, folded, yellow to deep tan* in colour.	*Favic chandeliers.*	*None.*	Occasional	Common in old colonies.
CANDIDA (*C. albicans*)	Intertriginous areas; paronychia; mucocutaneous junctions: tongue.	*Budding yeast cells and usually pseudohyphae.*	*Creamy, moist, honeycombed near centre.*	None.	None.	None.	*On corn-meal agar.*

Potato-carrot agar or beer-wort agar are also used to demonstrate special characteristics of the growth. All cultures are incubated at room temperature. Primary cultures should be made on media in slopes in one inch test tubes. Subcultures may be made in petri dishes to obtain larger colonies.

Material for culture is obtained in the manner described above. It is preferable to scrape the lesions with a dull scalpel and transfer the specimen directly to the medium. Several specimens collected in this way may be placed in one tube of medium by cutting across the surface of the agar several times with the scalpel. This procedure gives a high percentage of cultures free of contamination. If direct inoculation is not possible, the specimen may be placed in sterile glass or paper containers for transfer to the laboratory.

The rapidity, luxuriance and texture of the growth, the configuration of the surface and margin of the colony, the colours of the colony and the surrounding medium and the amount of growth under the surface of the agar should be noted from day to day. These characteristics vary with the species of the fungus, and identification can often be made on these findings. After prolonged growth many colonies become pleomorphic, developing a white fluffy aerial growth which interferes with identification. If colonies of saprophytic fungi appear, early subculture of the pathogenic fungus is necessary to prevent contamination and overgrowth by the saprophyte.

The microscopic characteristics of the growth of the ringworm fungi may be studied by suspending portions of the aerial growth in water or lactophenol cotton blue on a slide. Or subcultures from the original colonies may be made on thin films of agar on cover slips or in special culture chambers. The actual growth of hyphae and spores may be seen from day to day by this method. From this detailed information the exact identification of the genus and species of the fungus can be made.

The various members of the genus *"Candida"* cannot be differentiated by the appearance of the colonies on Sabouraud's agar nor by microscopic examination of the colonies. It is necessary to subculture the organism in streaks on corn meal agar. On this medium *"Candida albicans,"* the only pathogenic member of the genus, forms chlamydospores. Identification is based on this characteristic. To test the virulence of the organism, intravenous injection into rabbits of a heavy suspension of the fungus is used. *"Candida albicans"* produces a fatal septicaemia with characteristic pathological lesions in the lungs, liver, spleen and kidneys from which the organism may be recovered. Other members of this genus produce no symptoms or signs when injected.

Table I shows a summary of the appearances in tissues on direct examination and the gross and microscopic characteristics of the colonies of the fungi which are responsible for superficial infections. The diagnostic features of each species are shown in italics. The *"Trichophytons"* have been grouped into five types and a representative organism of each is shown.

ORTHOPAEDIC CARE DURING THE CONVALESCENT STAGE OF INFANTILE PARALYSIS

W. T. MUSTARD, M.D.

Treatment during the convalescent stage of poliomyelitis must vary with the extent of involvement of the central nervous system by the poliomyelitis virus. The virus attacks all parts of the brain and spinal cord, and, indeed other tissues such as the myocardium, and it is the purpose of this brief presentation to confine to those cases with involvement of those portions of the spinal cord controlling the musculature of the trunk and extremities.

The infectious stage is arbitrarily set at two weeks and this is generally regarded as the acute phase of the disease. The length of time, being arbitrary, may be considerably shorter or longer and convalescent care must vary with each case. If a good deal of pain and muscle spasm, as evidenced by stiff neck, hyperextended spine and limited straight leg raising, is present, rest, sedatives and heat in any form are indicated. As soon as possible after onset the limbs involved should be splinted in functional position to avoid contracture. This contracture in its most marked form of shoulder adduction and foot equinus may ensue early and delay the recovery in muscle long after the acute phase of the disease has passed. Prevention is the most effective method of treatment and the involved upper extremity should be splinted at 90° abduction of the shoulder, 90° flexion of the elbow and supination of the forearm. The paralyzed lower extremity should be splinted at 180° at hip and knee and 90° at the ankle. This splinting should be thorough and during the early stages the splints should remain on at least 20 out of the 24 hours. Joints should be put through a normal arc of motion and gentle massage may relieve muscle spasm and soreness when these are present.

After the acute stage of the disease is passed (and it may last for only a few days or it may persist as long as three months) one must assess the muscle involvement and grade the muscles according to any standard nomenclature in preparation for further therapy a a means of recording improvement. The muscle assessment which should be made 3-5 weeks after the onset of the disease is the base line on which stands the future care of the patient. If the trunk and all four extremities are involved the patient should be informed that at least six months convalescence in bed is indicated. The same is true if both lowers are involved or if one lower is severely effected. If the upper limbs show pareses it may be possible with proper splinting to reduce this six months bed rest to three. It is obvious from the foregoing that hospitalization of the paralyzed patient for at least three to six months after the acute attack is indicated.

It is during this six months bed rest under supervision that the capricious nature of the disease makes itself evident. Accurate muscle evaluations done once a month, although following a broad pattern, are as individual as the patient himself. There can be no doubt that, in common with other diseases, it is during this stage that the charlatan makes his reputation. Patients with identical paralysis at

one month may show in another three months totally different stages of recovery. This recovery varies not with the method of therapy but with the severity of the initial lesion. Recovery may be jeopardized if deformities develop in the muscles, fascia, ligaments and joint capsule before function in the central nervous system has resumed. Our therapy must therefore be directed along lines which assume that affected anterior horn cells in the cord are going to recover and the extremity must be prepared for this recovery.

In order to maintain the extremity in a state of preparedness we must above all prevent the development of any deformity. If all joints are put through a normal arc of motion daily it may be assumed that no deformity exists and the use of splints is simply an adjunct to therapy. If, however, a deformity is obviously present or develops insidiously the use of splints becomes a necessity and active correction of such deformities as equinus, hip flexion and forearm pronation should be carried out. In addition to the prevention of deformities and their correction if present, it is during this stage of disease that an attempt should be made to maintain the bulk of partially paralyzed muscles. This may be accomplished by careful active assisted motion within limits of fatigue and the physiotherapist may find hydrotherapy of great assistance in accomplishing this difficult form of therapy. The completely paralyzed muscle is a problem but fortunately (and unfortunately for the patient) solves itself. It has been the experience of most clinicians that the muscle completely paralyzed at the end of four months rarely recovers any useful function and that its bulk is not of any importance. If it recovers within this period (and many do within the first month) the problem of maintaining muscle bulk is the same as for the partially paralyzed muscle. Muscle atrophy in poliomyelitis is more an academic than a practical problem since the muscle which atrophies completely is the completely paralyzed muscle at the six months level and only in rare instances would recover any useful function. If completely paralyzed for one or two months and recovery takes place the atrophy present disappears as the muscle is treated as partially paralyzed.

It is during this stage of the disease that scoliosis may develop and the usual long curve with the pelvis acting in a compensatory manner to give a pelvic obliquity should be noted in order to follow its subsequent course.

At the end of six months patients with involvement of one or both upper extremities should be braced in a position of rest for paralyzed muscles and in a position of function. These patients may be discharged to follow-up clinics and during the the course of the next two years should carry on a regime similar to that in hospital and in addition attempt to strengthen slightly weakened muscles of importance by hypertrophy. At the termination of this period various corrective procedures may greatly impróve the function of the arm. The most successful of these being shoulder fusion, forearm flexor and apponens transplants.

Patients with one lower extremity involved and good arms and trunk if still recovering should be hospitalized until a plateau is reached in their muscle improvement and then adequately braced. Patients with both lower extremities involved should be hospitalized not only until they are adequately braced but until

they are able to use their braces for every day purposes. Orthopaedic procedures on the lower extremities are too numerous to list but stabilizing procedures should, in general, be postponed for one and a half to two years after the onset of the disease. The unfortunate few with both lower extremities and trunk involved may be forced to a wheel chair existence with only very brief sortees. And lastly that very small group wih all four extremities and trunk involvement becomes a problem for the patient and the community to solve.

Certain generalizations may be allowed which in no way can be considered rules in this peculiar disease. A totally paralyzed limb at three months will probably not recover much useful function. A spotty type of paralysis often shows remarkable recovery over the course of a few months. A muscle completely surrounded by normal muscles might completely recover even after three to six months. Occasional useful recoveries may be noted as long as one and a half to two years after the onset of the disease. The problem of convalescent care in poliomyelitis is an orthopaedic one in which the orthopaedist must rely on the neurologist, psychologist, physiatrist, physiotherapist, occupational therapist and play therapist for aid in the successful management of the disease.

PHYSICIANS' SERVICES INCOPORATED

R. H. SHEPPARD 4T8

In recent years there has been more and more discussion throughout the country of "State Medicine" and "Health Insurance." Various health programs have sprung up, some good, some bad. The latest of these in our own province is called "Physicians' Services Incorporated." It is an independent company established by a group of doctors and designed to bring health insurance to the people of Ontario.

The policies of the Corporation are guided by a Board of Governors elected annually by the members who are known collectively as the House of Delegates. This board consists of nine men, not more than three of whom may be laymen.

Its first president is Dr. Melville C. Watson and Mr. W. S. Major has been appointed General Manager. Branches supervised by an elected executive, the majority of whose members must be medical, are being organized throughout the province. The enrolling of Subscribers began on December 1st, 1947.

Any doctor of medicine licensed under the Medical Act of Ontario may become a member of the Corporation, as may any Certified Specialist. The basis for compensation of the Participating Physician is the schedule of minimum fees of the Ontario Medical Association. Any procedures not included will have fees fixed by the Corporation. Every month the physician submits his account for the services rendered to Subscribers along with reports of the conditions for which the services were rendered.

From the total sum paid by the Subscribers, the Corporation sets aside an amount necessary to pay for current operating expenses and to provide reserves. As this is a non-profit organization, the balance is set aside for the payment of accounts. This is done by dividing the accounts into "dollar units". The cash value of a unit will be determined by dividing into the total sum available for payment the total number of dollar units of approved accounts for services. Then payment of the cash value of the approved accounts will be made, but never of an amount greater than one dollar for each dollar unit. If the cash value of the unit doesn't equal $1.00, the difference will be paid out of any surpluses which will be released for the purpose by the Corporation. No extra charge may be made to the Subscribers.

The relation of doctor and patient is as always. A Subscriber is perfectly free to choose his General Physician and he in turn has the right to decline to provide services to any Subscriber in accordance with the present customs and practice.

Specialists' services are available for consultation and treatment on the advice of the General Physician. They receive special rates set by the Corporation. Payment of any outside physicians or specialists will be made by the Corporation according to the standard of fees laid down, but the Subscriber must pay any excess.

Available service include:

1. Diagnosis
2. Medical care during illness.
3. Obstetrical care.
4. Authorized consultations.
5. Authorized surgical services.
6. Treatment of fractures and dislocations.
7. X-ray, cystosocopic and bronchoscopic examinations, etc.
8. Anesthetics.
9. Preventive medical services such as inoculations.
10. Refractions only when done by a Participating Specialist.
11. Authorized radiation and physical therapy.

Not included are:

1. Provision of hospitalization, dental, ambulance and nursing services, drugs. vaccines, biological sera or extracts, eye glasses, special appliances, or oxygen.
2. Services entitling the Subscriber to care under the Workmen's Compensation Act.
3. Services when the Subscriber is in a sanatorium or hospital for tuberculosis, mental illness, alcoholism, epilepsy or drug addiction.
4. Cosmetic operations.
5. Operations for harmless conditions.
6. Mileage to practitioners rendering service.

Waiting periods exist before certain services are made available, for example, ten months for confinements, or six months for certain surgical procedures.

Subscription rates for one month:

Subscriber	$1.50
Subscriber and 1 Dependent (Husband, Wife, and Child)	3.50
Family Rate	5.00

Each Subscriber bears an identification card which must be presented to the physician on applying for care. A month's written notice is all that is required in order to voluntarily terminate the agreement. Default of payment of course will terminate it at once.

A Surgical and Obstetrical Services contract is available with the following subscription rates:

Subscriber	$ .75
Subscriber and 1 Dependent (Husband, Wife and Child)	1.75
Family Rate	2.50

On examining the structure of this plan, one can see that it has received much thought and consideration. It will provide a high level of medical service to the people of Ontario at quite reasonable rates. One might argue that the doctor's income will be reduced by having to charge minimum rates, but the increase in the

number of payments that he actually receives will more than make up the difference. One of the biggest advantages of this scheme is the complete freedom under which the doctors and patients work—there is no compulsion anywhere.

The quality of one physician's work may be far above that of another yet each will receive the same fee. This state of affairs is seen wherever Medicine is practised and the only way this can be rectified apart from its recognition on the part of the patient is by some medical inspection system. This is not, however, a particular problem in this health scheme.

And so the plans have been drawn up, but the success or failure of this worthy enterprise rests upon the shoulders of the general practitioner. Conscientious physicians giving it their full support will make it a success.

REFERENCE

The Ontario Medical Review *14*: 109-129, December 1947.

IT'S EASIER FOR INFANTS TO DIGEST--

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Feature

R. K. GRAHAM, Editor

TRAINING OF A PHYSICIAN

R. F. FARQUHARSON
Professor of Medicine

At the beginning of a discussion on the training of a physician it should be pointed out that physicians share with general practitioners the responsibility for the understanding, diagnosis and treatment of their patients as persons: a study of the whole patient is essential at all stages of medical training.

Internal medicine is a broad subject and no one can master all the technical details of special diagnosis and treatment. Accordingly, most physicians ultimately make a more intensive study of some special branch; this allows the development of greater skill in certain narrower fields while maintaining the broader interests and responsibilities that are essential for medical diagnosis and treatment.

The modern trends in medical practice and its relation to the State and other corporate bodies have emphasized the need for some recognized standard by which doctors with special qualifications may be listed and known. In Canada this need has been met by the foundation and growth of the Royal College of Physicians and Surgeons and by the certification of specialists by that College. Two different standards of qualification have come into being: (1) Fellowship in the Royal College in Medicine or in Surgery; and (2) Certification of Specialists in Medicine or Surgery and in certain Specialties. Of these, the Fellowship is the higher qualification and its acquisition automatically confers certification in the appropriate Specialty. It is the hope of many responsible parties that at some future date certification in Medicine and Surgery and their branches will be attainable only through Fellowship in the Royal College.

In an attempt to establish and maintain a high standard of practice the Royal College has specified certain essential requirements for graduate training which must be fulfilled before a physician is accepted as a candidate for either examination. The course of graduate training in Medicine covers a period of at least five years, which includes one year's junior rotating interneship and two years as senior interne, assistant resident or resident in Medicine in approved hospitals organized for graduate training. Those proceeding to the certification examinations may spend the remaining two years either in the further study or in the study and practice of internal medicine. Those proceeding to the Fellowship examinations must spend all five years in study and training; the last two years may, however, be spent in a number of different ways, including further training and research as residents or Fellows in Medicine, training in approved special hospitals such as sanatoria for tuberculosis, psychiatric hospitals, etc., training and research in the basic sciences of biochemistry or physiology or in anatomy or pathology, or in an approved course of study at home or abroad.

A modified Fellowship examination in Medicine may be taken by those who have had special training in one of the following specialties: Dermatology and Syphilology, Neurology and/or Psychiatry, Paediatrics, and Radiology. All Specialists must, however, have taken a general interneship and spent one year as a senior interne in Medicine in addition to taking an adequate training in their special field.

A knowledge of the basic medical sciences necessary to the proper understanding of internal medicine and its special branches is required of all candidates. This applied knowledge may be acquired by attendance at an organized course of instruction in basic medical sciences (which may be taken on a part time basis) or by spending a year or more as a Fellow in clinical or fundamental science departments or in pathology or anatomy,—appropriate courses of study in the wider fields may be necessary in addition. Those going into academic work are strongly advised to spend a year in research work in a laboratory science and to acquire further training in clinical research in a Department of Medicine organized for research and study of disease by scientific methods.

The Royal College has accepted responsibility for the approval of Canadian Hospitals for graduate training and the work is now in progress. Ultimately there will be published information about Canadian hospitals, indicating in which subject or subjects approval for graduate training has been given to each.

It should be pointed out that the door of admission to either Certification or Fellowship examinations is not closed on the doctor who is unable to take extensive training immediately after graduation. In such cases training taken on a part time basis over a longer period of time and experience gained in practice are assessed by the committee of the College that deals with credentials. Further appropriate training may be necessary to supplement the initial interneship and longer experience in practice; the plan is elastic, not rigid.

Principles of Training

It cannot be too strongly emphasized that training is not an acquisition of special technique only, but rather a continued study in the methods of thought and critical judgment while learning the application of basic sciences and acquiring the technique of history-taking, physical and laboratory examinations and various methods of treatment,—all leading to a broad medical education. To conform to the requirements of the Royal College is not enough. These requirements form only a framework: they provide general direction, a plan or a pathway that may be followed. The real job of training is done by the trainee. Unless he concentrates his energies and devotes his whole being to this study he cannot hope to reach the goal. He cannot be carried; he must make his own way. He may be directed and helped and encouraged by skilful teachers, but he must learn for himself.

The physician must observe, examine and analyse again and again till the processes become second nature. He must constantly study people: his patients and others. By taking history after history with precision and exactness of detail,

and discussing these matters with one's associates, one comes to know more and more, but never to master what Sydenham called the 'natural history of disease'. By enquiring carefully into disturbances of function in health and disease one learns for oneself, in a way no other person can teach it, how to tell the normal from the abnormal, the healthy state from the diseased, whether the anomaly is significant or not, whether certain symptoms are physiological or pathological, the effects of emotion, environment and many other influences. All these are learned only by the constant study of patients. As John Brown said: "Symptoms are universally available; they are the voice of nature." But many histories must be taken carefully and many patients followed for long periods before that language is well understood, and even with persistent life-long study the understanding is never complete.

If one trains in hospitals where the staff are interested in fundamental physiological and pathological processes and in the study of the natural history of disease, one can gradually acquire methods by which he can continue the study; one learns to evaluate remedies new and old and to assess the effects of emotions and other influences. At the same time one learns the special techniques required and links them intimately with one's philosophy and action. The well-trained physician has a basis for future growth; he will continue to widen his knowledge and to acquire the breath of understanding and philosophy that makes him a wise counsellor. If the graduate fails to learn proper methods of study of patients and analysis of detailed information and to acquire sound clinical judgment, no mastery of any special technique will ever make him a good physician. It is the fundamental training and philosophy that matters; the special technique is important but to a lesser degree; the passing of higher examinations is only a sign that certain hurdles have been passed and that the physician has acquired a certain amount of information from his long training. As the late President Mazaryk of Czechoslovakia remarked: "A pile of certificates is still no guarantee of education, and by no means do they replace natural talents; . . . book-learning, titles and degrees are no guarantee for decency, honour or courage. A man needs experience of life; . . . nor is cleverness enough—as in all things, it is the worth of the whole man that matters."

Abstracts

E. R. YENDT, Editor

List of Contributors:

H. M. Broder
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SURGERY I

The Role of Vascular Spasm in Recovery of Strangulated Intestine. Experimental Study. H. Laufman and H. Method: *Surg. Gyn. & Obs., 85*: No. 6.

The recovery of strangulated intestine was investigated from the standpoint of the behaviour of the involved vasculature. Evidence obtained by intestinal surface temperature readings, indicates that there is considerable residual vasospasm in the minute vessels of a still viable loop. Of the many factors which affect the recoverability of strangulated intestine, vasospasm is of no small significance, whether the strangulation be primarily arterial or venous.

An arterial type strangulation retains recoverability more than five times as long as does the venous type. By the time an arterial strangulation assumes the gross appearance of a venous type, its vasculature has lost al reactivity and is beyond recovery. In non-viable segments of either type, release of the strangulation results in a poor temperature response or an actual decline in temperature.

The response of intestinal surface temperature to the various forms of resusticative therapy is offered as a simple test for viability which may have some clinical application. The rise in temperature of the affected loop as compared to normal bowel is an indication as to its recoverability.

Comparative studies between the effects of warm packs, oxygen inhalations, mesenteric novocaine injections, and intravenous injections of papaverine hydrochloride were attempted. All were found to be of some value in increasing the blood flow through a still viable loop. When papaverine in large doses was given following on or combination in combination with the first three measures, an additional response was usually seen.

H. M.B.

SURGERY II

Causalgia. F. M. Mayfield: *Amer. Jour. of Surg., 74*: No. 5.

This is essentially a report on a comprehensive study of peripheral nerve injuries by both British and American Services during world war two. It is now believed that the majority of painful post-traumatic dystrophies, with the exception of painful amputation stump and true hysteria, are expressions of the same underlying disorder.

From a summary of over 100 cases of true causalgia, the following conclusions are drawn: (1) a penetrating wound involving a large peripheral nerve was the initiating factor in each case, (2) the outstanding complaint was a burning pain, onset of which was instantaneous in 50% of cases, and delayed from 14 hours to 3 months in the remainder, (3) median and sciatic nerves are most commonly involved, (4) none was associated with injury to major blood vessels, (5) infection of the wound was rarely encountered.

It is suggested that the painful mechanism involved, consists of a shunt of sympathetic impulses of all sorts into the sensory fibres at the site of injury to a mixed nerve.

The disease was observed in approximately 5% of all patients admitted with peripheral nerve wounds. While pain was continuous, it was aggravated by emotional stimuli such as anger, fear and disturbing noises. Two types of associated vaso-motor upsets were encountered: (a) vasoconstriction, (b) vasodilatation. Twenty percent showed spotty osteoporosis of the small bones of the involved extremity.

Diagnosis can be established by appropriate sympathetic chain block with procaine. It appears that although repeated injections may provide relief, in the majority of cases, permanent relief is established only by complete sympathectomy of the involved part.

H. M. B.

PAEDIATRICS I

Excretion of Drugs in Human Milk. N. Sapeika: *J. Obstet. Gynec. Brit. Empire, 54,* 426-431 (1947).

In this review of the literature relating to the excretion of drugs in human milk, Sapeika reports that many of the observations made by Reed in his review published in 1908 are still valid. Two of these which the literature from that time have continued to verify are (a) it is rarely necessary to remove the child from breast feeding while the mother is receiving drug therapy, and (b) it is rarely desirable to treat a child with drugs given to the mother.

Reed concluded that alcohol, opium, chloroform, ether, thyroid, and lead should be used with caution, and that atropine, antipyrine, phenacetin, chloral hydrate, arsenic, bismuth, mercury or copper compounds, castor oil, senna, quinine, bromides, iodides, salicylic acid and copaiba pass into the breast milk in small quantities. In his review of the literature published since 1908, Sapeika has found evidence that (a) unusually large amounts of alcohol administered to the mother have been found to influence the nursling, (b) barbiturates are excreted in the milk but usually in amounts too small to affect the infant, (c) bromides may be excreted in quantities sufficient to cause skin eruptions in infants, (d) no morphine was found in the milk of an addict taking 20 grains per day, but a trace was present in the milk of a normal woman seven and one half hours after the administration of one quarter of a grain of the alkaloid, (e) excessive smoking

has caused a decrease in milk secretion and nicotine may be detected in the milk, (f) nicotine intoxication resulting from working in factories or from excessive smoking may affect the mother and also the child, (f) conjugated phenolphthalein may be found in breast milk following the taking of phenolphthalein by the mother, but it has not been observed to have any effect on the bowels of the nursing infant, (g) the active constituents of senna, cascara, or rhubarb are excreted in the milk and may produce purgation in the infant, and (g) sulphonamides may attain higher levels in the milk than in the blood but the amount ingested by the infant is too small to be dangerous.

W. G. B. C.

PAEDIATRICS II

Appendicitis in the Young Child. H. Williams: *Br. Med. Jl. 1947*, 730-732.

Appendicitis in children below three years of age is not uncommon, but is frequently overlooked, and is diagnosed only after complications have arisen. The mortality of this condition can be lowered by early diagnosis and prompt treatment. Williams presents a series of cases of appendicitis from the Melbourne Children's Hospital. Of 1487 children treated for acute appendicitis between 1935 and 1940, 42 were under the age of three years, 1 was under 1 year, 11 were between 1 and 2 years, and 30 were between 2 and 3 years of age.

There were many complications in this age group. Only 6 cases were uncomplicated. 21 had a local peritonitis and 15 had general peritonitis. 7 of these 15 subsequently died. The large number of complications were probably due to the long interval between onset and diagnosis, the rapid progression of gangrene and perforation, and the inefficiency of the immature omentum to wall off the infection.

The most prominent clinical features were abdominal pain and vomiting. The pain could not be localized due to the age of the patients but was ascertained by the patients' reactions. The finding of constipation was inconstant and seen in only 14 cases. Half of the patients had normal movements, while 9 had diarrhoea. In the cases with pelvic peritonitis, frequency and pain on micturition were also noted.

The examination of these young patients required much gentleness and patience. Tenderness in the right lower quadrant, or in the right suprapubic area associated with overlying rigidity were almost constant findings. The tenderness was detected by the wincing of the patients' faces. One half of the cases also presented a firm discrete, slightly mobile mass in the area of tenderness. The cases with general peritonitis showed moderate abdominal distension. This was also seen in some cases of local peritonitis. Rectal examination was useless in locating tenderness but helpful in localizing the mass. The pulse rate and temperature were not diagnostic and varied from case to case. The diagnosis of acute appendicitis was made on the history of pain in the abdomen and vomiting, and on the finding of localized abdominal tenderness and rigidity.

Surgical intervention was instituted as early as possible in all cases. All patients with masses or generalized peritonitis were left with drainage. The semi-Fowler position was used postoperatively. One-third of the patients also received sulphonamides. Of the 42 cases, 8 died, all due to general peritonitis.

M. G. W.

SURGERY III

Effects of Supradiaphragmatic Section of Vagus Nerves in Man. W. B. Crandell W. E. Boehm, J. H. Mulholland: *Arch. Surg. 55,* 343 (1947).

Crandell and his co-workers studied a group of patients with peptic ulcers who were undergoing treatment by supradiaphragmatic section of the vagus nerves. The following facts were established by preoperative and postoperative tests: (1) The secretion of acid into the stomach in response to the intravenous or intragastric administration of alcohol appears to be diminished after sectioning of the vagi; (2) The electroencephalogram of a patient with peptic ulcer is not altered by section of the vagi; (3) Nitrogen balance studies did not reveal any impairment of protein absorption or utilization following section of the vagi; and (4) There is clinical and X-ray evidence of decreased gastric motility following section of the vagi.

W. G. B. C.

MEDICINE

Diseases of the Salivary Glands. A. C. Furstenberg: *J. Amer. Med. Assn. 136,* 1 (1948).

The etiologic factors responsible for inflammations of the salivary glands are (a) foreign bodies, particularly calculi, (b) injury or disease of the abdomen or pelvis, and (c) extension of infection from neighbouring tissues. Injury and dehydration are also potent influences in the origin and development of infections in these structures.

Effective agents in the therapeutic armamentarium are sulphadiazine and penicillin. Hydration must be instituted and maintained. Wide incision and massive drainage are required when a circumscribed collecton of pus is present.

Chronic infective granulomas are rare manifestations of disease of the salivary glands. A noncaseating form of tuberculosis is occasionally observed. The gumma, perhaps, is more rarely seen. Actinomycosis has responded most satisfactorily to the sulphonamide drugs and penicillin therapy.

A dysfunction of the salivary glands is occasionally the result of end organ lesions of the peripheral secretory nerves. A normal salivary flow, under such conditions, may be produced by the administration of pilocarpine. The effect of the drug is augmented by the simultaneous ingestion of the acid-forming salt, ammonium chloride.

The common neoplasm of the salivary glands is the mixed tumor. The soft tumors are more prone to exhibit carcinomatous alterations than the hard, firm ones. They are devastating in their clinical behaviour in that they tend to degenerate into rapidly proliferating carcinomata. Surgical intervention which accomplishes the complete removal of the lesion is most successful. When these tumors do recur, however, they usually present frank carcinomatous alterations and further surgical efforts are futile.

W. G. B. C.

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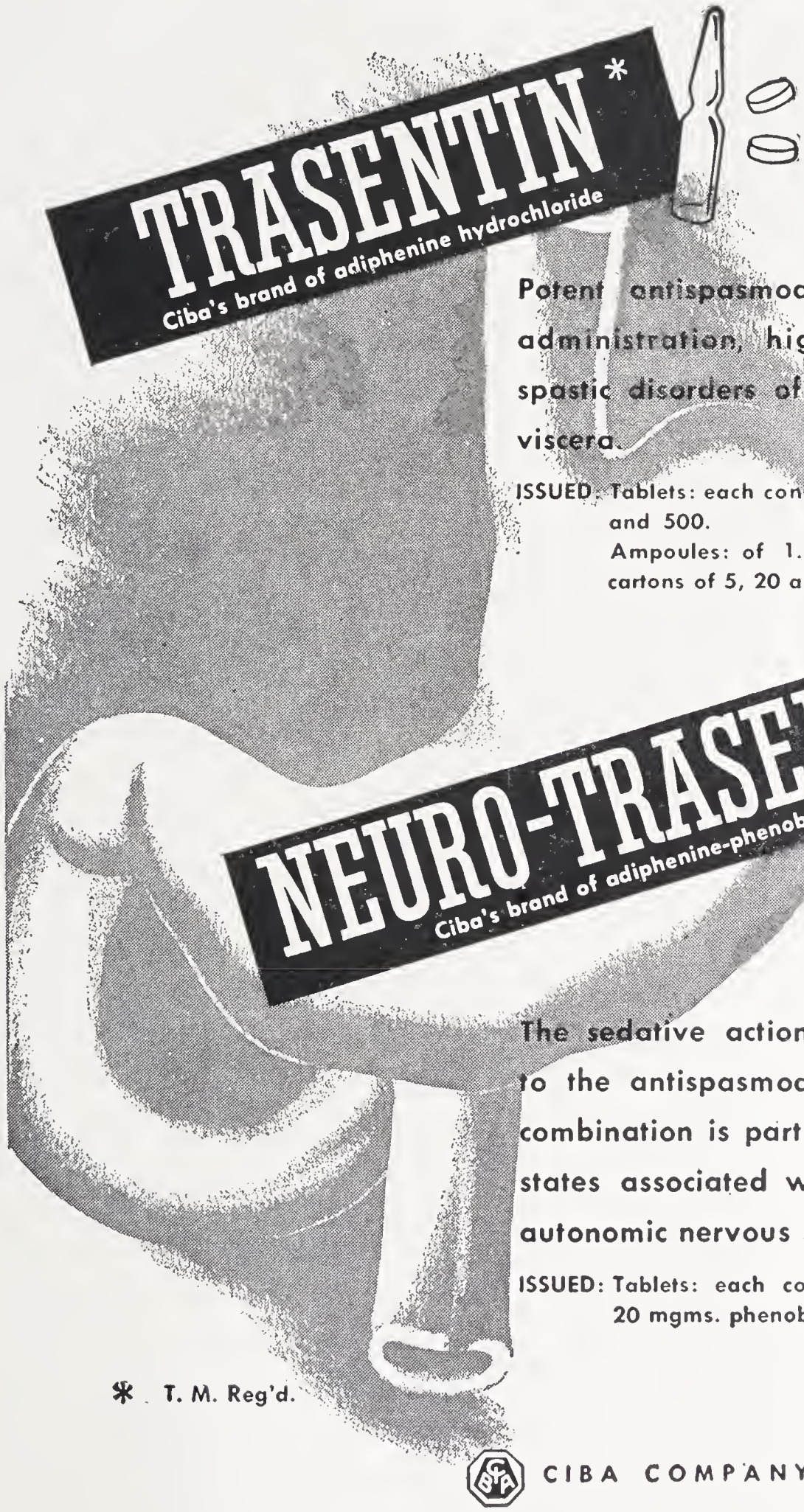

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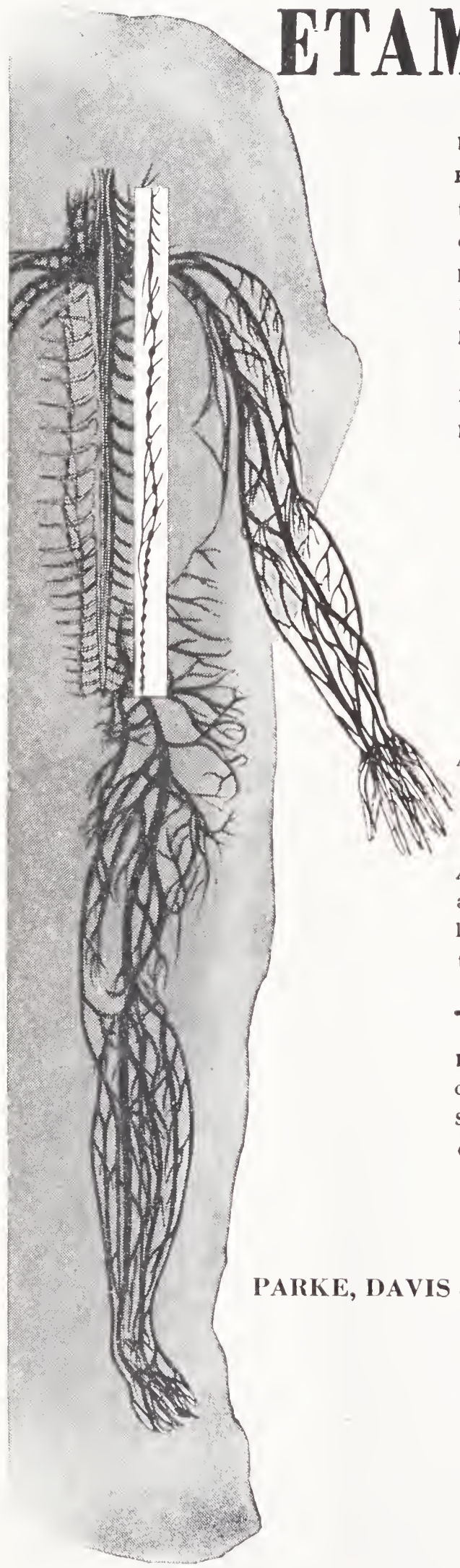

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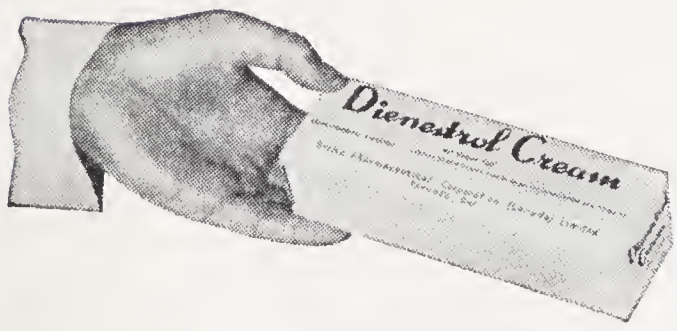

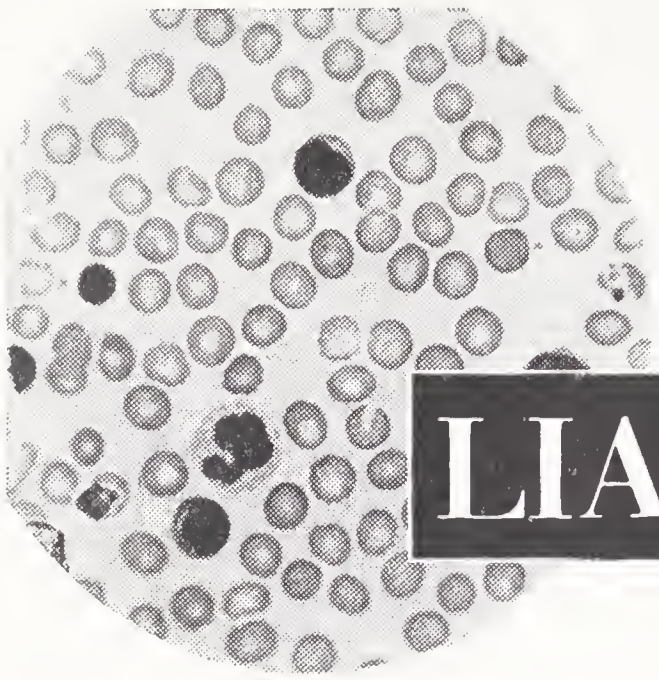

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